Sulfur–Containing Amide–Based [2]Rotaxanes and Molecular Shuttles

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Abstract: We report the synthesis, structure and properties of [2]rotaxanes prepared by the assembly of benzylic amide macrocycles around a series of amide and sulfide-/sulfoxide-/sulfone-containing threads. The efficacy of rotaxane formation is related to the hydrogen bond accepting properties of the various sulfur-containing functional groups in the thread, with the highest yields (up to 63% with a rigid vinyl spacer in the template site) obtained for sulfoxide rotaxanes. X-Ray crystallography of a sulfoxide rotaxane, **5**, shows that the macrocycle adopts a highly symmetrical chair-like conformation in the solid state, with short hydrogen bonds between the macrocycle isophthalamide NH-protons and the amide carbonyl and sulfoxide S-O of the thread. In contrast, in the X-ray crystal structures of the analogous sulfide (**4**) and sulfone (**6**) rotaxanes the macrocycle adopts boat-like conformations with long intercomponent NH···O=SO and NH···S hydrogen bonds (in addition to several intercomponent amide-amide hydrogen bonds). Taking

advantage of the different hydrogen bonding modes of the sulfur-based functional groups, a switchable molecular shuttle was prepared in which the oxidation level of sulfur determines the position of the macrocycle on the thread.

Introduction

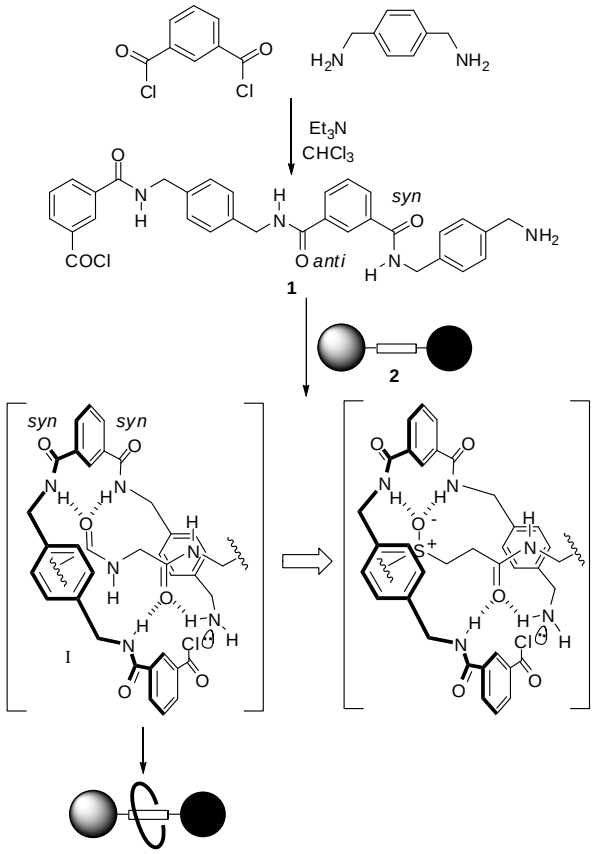
Since the hydrogen bond directed synthesis of the first amide [2]catenanes[1] and rotaxanes,[2] significant improvements have been made in the efficiency of their preparation and their structural diversity.[3-11] Although the majority of hydrogen bond accepting groups used in the construction of benzylic amide macrocycle-based catenane and rotaxanes have been either amide[3] or ester[3e,4] functionalities, recently attention has turned to the use of alternative hydrogen bond accepting moieties in the thread, such as squaraines,[5] phenolates,[6] ureas,[7] pyridones,[8] nitrones,[9] azodicarboxamides[10] and ion-pair[11] motifs. The highly polarized S-O bond of sulfoxides is an attractive moiety for inclusion in interlocked structures, not only because of its superior hydrogen bonding acceptor properties (compared to amides[12]) but also due to the relative ease by which the sulfoxide moiety can be both oxidized and reduced, enabling the hydrogen bond properties of the functional group to be significantly varied. Here we exploit these features in the synthesis of a range of simple sulfide-, sulfoxide- and sulfone-containing [2]rotaxanes, and in the construction of a bistable molecular shuttle in which the oxidation level of the sulfur atom alters the position of the macrocycle on the thread.

Results and Discussion

Simple dipeptide,[3a] fumaramide[3e] ((*E*)-NHCOCH=CHCONH-) and succinamide[3e] (-$NHCOCH_2CH_2CONH$-) motifs are effective templates for rotaxane formation because their hydrogen bond accepting carbonyl groups are well positioned to direct the assembly of a benzylic amide macrocycle around the template site via five-component 'clipping' reactions (Scheme 1). These reactions produce

interlocked architectures because multipoint hydrogen bonding between the open-chain precursor **1** (which in the absence of a suitable template preferentially adopts a linear *syn-anti* conformation) and the thread **2** promotes a conformational change that brings the reactive end groups close together (Scheme 1, I), leading to rapid cyclization of **1** about the axle.[2b,3a,e] Given the geometric requirements of the multipoint hydrogen bonded intermediate I, we were intrigued as to whether it would be possible to exchange one of the sp^2-hybridized amide groups in the template for an sp^3-hybridized sulfur atom in any or all of its oxidation levels (sulfide, sulfoxide, sulfone), each of which exhibit different hydrogen bond accepting characteristics.[13]

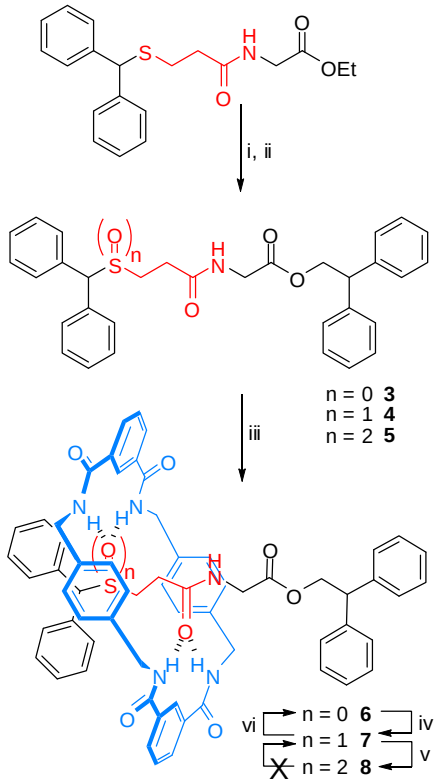
Scheme 1. Hydrogen Bonding Modes of Bis-Amide and Sulfoxide-Amide Templates for Rotaxane Synthesis.



An appropriate sulfide thread **3** was synthesized in four steps from commercially available 3-mercapto-propionic acid (see Supporting Information and Scheme 2). Oxidation of **3** with *m*-chloroperoxybenzoic acid (MCPBA) could be used to afford either the sulfoxide (**4**) or sulfone (**5**) threads in good yields

(Scheme 2, step ii). The three threads (**3-5**) were each subjected to rotaxane-forming conditions[3a] using equimolar amounts of isophthaloyl dichloride and *p*-xylylenediamine in $CHCl_3$ in the presence of Et_3N, pleasingly yielding the desired [2]rotaxane, **6-8**, in each case. The sulfoxide rotaxane **7** was isolated in 43% yield (cf. 62% and 50% for glycylglycine[3a] and succinamide threads[3e] using similar rotaxane-forming protocols) whereas the yields of the sulfide **6** (12%) and sulfone **8** (10%) rotaxanes were considerably lower, presumably due to the modest hydrogen bond acceptor ability of those functional groups.

Scheme 2. Synthesis of Sulfur-Containing Hydrogen Bonded [2]Rotaxanes **6-8**[a]



[a] Reagents and conditions: (i) diphenylethanol (1.0 equiv.), *bis*(chlorodibutyltin)oxide (cat.), toluene, reflux, 8 h, 88% (**3**); (ii) MCPBA, $CHCl_3$, –20 °C, 90 min, 70% (**4**, 1.0 equiv. MCPBA), 98% (**5**, from **4**: 1.0 additional equiv. MCPBA); (iii) isophthaloyl dichloride (five-fold excess), *p*-xylylenediamine (five-fold excess), Et_3N (ten-fold excess), $CHCl_3$, RT, 4 h, 12% (**6**), 43% (**7**), 10% (**8**); (iv) MCPBA (1.0 equiv.), $CHCl_3$, –20 °C to RT, 90 min., 95%; (v) MCPBA (1.0 equiv.), $CHCl_3$, –20 °C to RT, 90 min., 97%; (vi) Lawesson's reagent (1.0 equiv.), THF, –20 °C to RT, 1 h, 87%.

Small crystals of each of the three sulfur-containing rotaxanes **6**-**8** were obtained by slow diffusion of diethyl ether into saturated solutions of the rotaxanes in methanol (**6**), dichloromethane (**7**) or chloroform (**8**) and their solid state structures determined by X-ray crystallography (Figures 1-3).[14] The crystal structure of the sulfoxide–amide [2]rotaxane **7** (Figure 1) has features reminiscent of the solid state structures of various bis-amide thread (dipeptide,[3a] fumaramide,[3e] succinamide[3e]) rotaxanes. The benzylic amide macrocycle adopts a low energy chair-like conformation with each isophthalamide group hydrogen bonding to the thread sulfoxide or carbonyl group through four short (2.12-2.56 Å NH···O) hydrogen bonds. The isophthalamide–sulfoxide hydrogen binding is sufficiently strong that it overcomes the problem of shape of the sp^3-hybridized sulfoxide group, twisting the conformation of the thread in order to ensure the necessary relative positioning of the hydrogen bonding groups.

In contrast, in the solid state structures of the sulfide–amide (**6**) and sulfone–amide (**8**) rotaxanes (Figures 2 and 3, respectively), the macrocycle adopts relatively high energy conformations that maximize the number of intercomponent amide–amide hydrogen bonds (presumably because amide–sulfide and amide–sulfone hydrogen bonds are intrinsically weak). The strength of the amide–amide hydrogen bonding distorts the macrocycle into boat-like conformations with only a single (2.77 Å NH···S (**6**); 2.15 Å NH···OS(O) (**8**)) intercomponent amide–sulfide/sulfone hydrogen bond in each case (together with three intercomponent amide-amide hydrogen bonds).

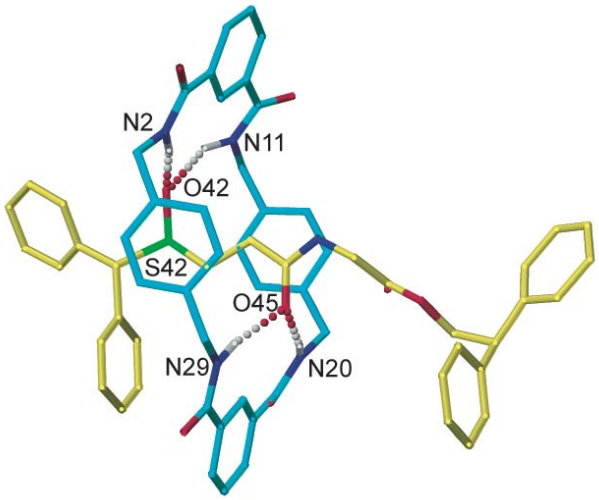


Figure 1. X-Ray crystal structure of sulfoxide [2]rotaxane **7**. Hydrogen bond lengths [Å]: O42-H2N = 2.38; O42-H11N = 2.56; O45-H29N = 2.12; O45-H20N = 2.31. Hydrogen bond angles [°]: N2-H2N-O42 = 127.3; N11-H11N-O42 = 142.2; N20-H20N-O45 = 148.7; N29-H29N-O45 = 171.7.

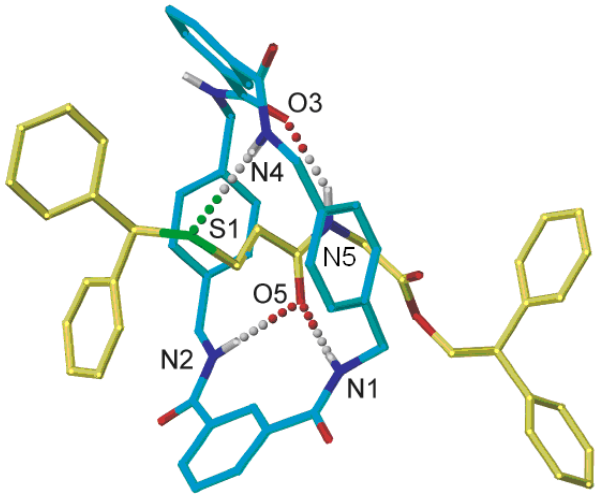


Figure 2. X-Ray crystal structure of sulfide [2]rotaxane **6**. Hydrogen bond lengths [Å]: S1-H4N = 2.77; O3-H5N = 2.18; O5-H1N = 2.21; O5-H2N = 2.30. Hydrogen bond angles [°]: N1-H1N-O5 = 160.6; N2-H2N-O5 = 172.1; N4-H4N-S1= 151.6; N5-H5N-O3 = 151.3.

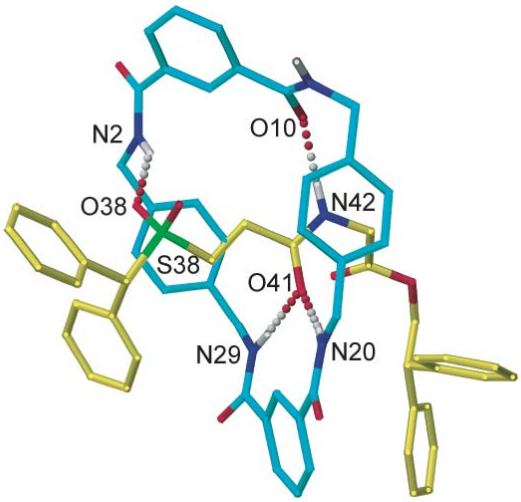


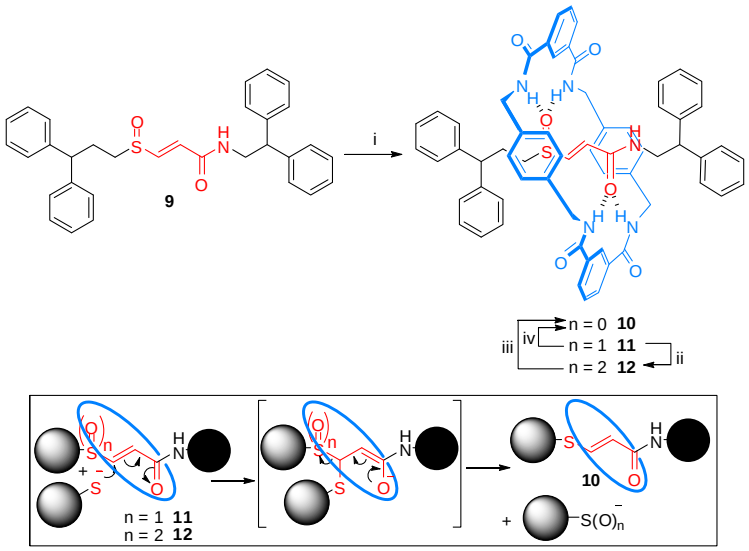
Figure 3. X-Ray crystal structure of sulfone [2]rotaxane **8**. Hydrogen bond lengths [Å]: O38-H2N = 2.15; O10-H42N = 1.97; O41-H20N = 2.07, O41-H29N = 2.22. Hydrogen bond angles [°] N2-H2N-O38 = 143.3; N42-H42N-O10 = 153.5, N20-H20N-O41 = 159.6; N29-H29N-O41 = 175.1.

The difference in hydrogen bonding behavior of these motifs suggested that it might be possible to modulate the strength of the intercomponent binding in such rotaxanes by chemically switching the oxidation level of the sulfur-based functional group. Using MCPBA, the sulfide rotaxane **6** could be oxidized to either the sulfoxide **7** or sulfone **8** rotaxanes, depending on the stoichiometry of the peroxy acid used, and the sulfoxide rotaxane **7** similarly converted into sulfone **8** (Scheme 3). However, although sulfoxide **7** could be reduced to sulfide **6** using an excess of Lawesson's reagent ($(CH_3OC_6H_4PS_2)_2$),[15] chemical reduction of the sulfone rotaxane **8** could not be achieved. The inability to reduce sulfone **8**, as well as the modest template ability of the flexible threads, led us to consider the use of a more rigid vinyl sulfoxide-based template. This could allow the substitution of a sulfoxide or sulfone functionality by Michael addition of a nucleophile and subsequent elimination of the sulfoxide/sulfone fragment.[16] If the nucleophile used is the thiolate analogue of the rotaxane stopper then this Michael-retro-Michael sequence could be employed to afford the 'reduced' sulfide–amide rotaxane (Scheme 3, inset).[17]

Vinyl sulfoxide–amide thread **9** was prepared in three steps from commercially available building blocks (see the Supporting Information). The bulky diphenylmethyl group of **9** is positioned further away from the sulfur center in comparison to threads **3-5** in order to minimize steric interactions between the macrocycle

and the stopper. Rotaxane formation using the standard clipping protocol afforded the vinyl sulfoxide rotaxane **11** in 63% yield (Scheme 3), significantly higher than for the flexible sulfoxide thread (**4**) and similar to that of other well-positioned hydrogen bond acceptors on rigid threads (fumaramide,[3e] *bis*-nitrone,[9] azodicarboxamide[10]). Oxidation of **11** with MCPBA generated the vinyl sulfone rotaxane **12**. Treatment of either **11** or **12** with excess sodium 3,3-diphenylpropan-1-thiolate in hot DMF allowed complete and clean conversion to the vinyl sulfide [2]rotaxane **10**. Presumably Michael addition of the thiolate stopper on the α-β-unsaturated amides of **11** and **12** generates the corresponding amide enolates (Scheme 3, inset), stabilized through hydrogen bonds with the amide macrocycle. Subsequent β-elimination forms the vinyl sulfide rotaxane **10**.

Scheme 3. Synthesis of Vinyl Sulfur-Based Hydrogen Bonded [2]Rotaxanes **9**-**12**[a]

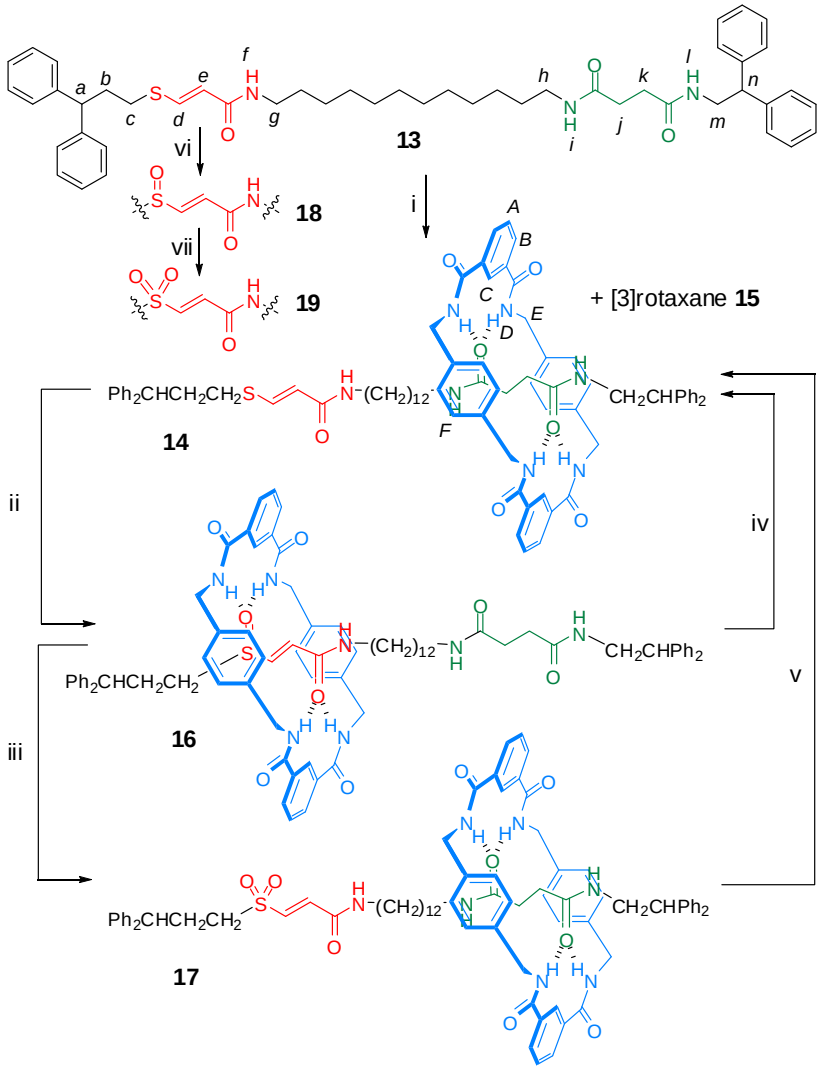


[a] Reagents and conditions: (i) isophthaloyl dichloride (five-fold excess), *p*-xylylenediamine (five-fold excess), Et_3N (ten-fold excess), $CHCl_3$, RT, 63% (**11**); (ii) MCPBA (1.5 equiv.), CH_2Cl_2, RT, 18 h, 83% (**12**); (iii) $Ph_2CHCH_2CH_2SNa$ (10 equiv.), DMF, 120 °C, 85% (**10**); (iv) $Ph_2CHCH_2CH_2SNa$ (10 equiv.), DMF, 120 °C, 16 h, 92% (**10**). Inset: Mechanism for the Michael-retro-Michael substitution of the sulfoxide/sulfone stopper group.

The significant difference in binding modes of the amide-sulfur group binding sites led us to incorporate the vinyl sulfur hydrogen bonding motif into a more complex structure in which chemical oxidation/reduction of the sulfur moiety could be used to induced shuttling of the macrocycle between two different sites of the rotaxane thread.[18] Various external stimuli, including pH,[19] metal ions,[20] photochemistry,[21] electrochemistry,[22] temperature[23] and the reversible formation (and breaking) of C-C bonds,[24] have been used to induce shuttling in bistable amide rotaxane switches. However, the use of chemical (rather than electrochemical) oxidation and reduction to induce shuttling in rotaxanes remains rare.[10] Here the design of the rotaxane thread consists of both an oxidation-level-tuneable sulfur-based binding site and a flexible succinamide group (Scheme 4). The macrocycle preferentially binds to the sulfoxide moiety over the succinamide station due to the superior hydrogen bonding strength of the S-O bond and the rigidity of the vinyl spacer between the amide and sulfoxide hydrogen bond accepting groups.[21c] Chemical reduction or oxidation to the corresponding sulfide or sulfone switches off the strong hydrogen bonding to the sulfur functional group and the macrocycle relocates to the succinamide binding site.

The synthesis of a vinyl sulfide-succinamide thread, **13**, was achieved in four steps from commercially available starting materials (see the Supporting Information). Formation of the interlocked architecture using the multi-component clipping reaction furnished a mixture of [2]- and [3]-rotaxanes, **14** and **15**, which were separated by flash column chromatography. [2]Rotaxane **14** could be smoothly and selectively oxidized to the corresponding vinyl sulfoxide **16** or vinyl sulfone **17** rotaxane, depending upon the stoichiometry of oxidant used. The corresponding sulfoxide and sulfone threads **18** and **19** were prepared by oxidizing **13** with MCPBA (Scheme 4).

Scheme 4. Synthesis and Switching of a Sulfur–Succinamide Molecular Shuttle[a]



[a] Reagents and conditions: (i) isophthaloyl dichloride (five-fold excess), *p*-xylylenediamine (five-fold excess), Et_3N (ten-fold excess), $CHCl_3$, RT, 23% **14** + 8% **15**; (ii) MCPBA (1.0 equiv.), CH_2Cl_2, -78 °C to RT, 2 h, 90%; (iii) MCPBA (2.0 equiv.), CH_2Cl_2, -78 °C to RT, 2 h, 92%; (iv) $Ph_2CHCH_2CH_2SNa$ (10 equiv.), DMF, 120 °C, 16 h, 93%; (v) $Ph_2CHCH_2CH_2SNa$ (10 equiv.), DMF, 120 °C, 18 h, 90%; (vi) MCPBA (1.0 equiv.), CH_2Cl_2, -78 °C to RT, 2 h, 93%; (vii) MCPBA (2.0 equiv.), CH_2Cl_2, -78 °C to RT, 2 h, 88%.

Comparison of the ^{1}H NMR spectra of the three oxidation states of the vinyl sulfur rotaxanes **14**, **16** and **17** in $CDCl_3$ with the corresponding free threads allowed the net position of the macrocycle to be determined in each case. With the vinyl sulfide **14** and vinyl sulfone **17** rotaxanes, the chemical shift of the signal corresponding to the ethylene bridge of the succinamide station are significantly shifted upfield (Figure 4b and 4f, respectively) due to shielding from the xylylene rings of the macrocycle, whereas signals

from the vinyl sulfide and sulfone moieties do not undergo large shifts between thread and rotaxane, consistent with the macrocycle being predominantly located over the succinamide binding site. In contrast to rotaxanes **14** and **17**, the resonances of sulfoxide rotaxane **16** are broad at room temperature in $CDCl_3$, indicative of slow dynamic processes, presumably a result of stronger intercomponent hydrogen bonding in the sulfoxide shuttle. At 55 ºC the resonances are comparable in sharpness to the other rotaxanes at room temperature (Figure 4d). Modest shielding of the protons of the succinamide station (Δδ 0.2 ppm) occurs in sulfoxide rotaxane **16** (Figure 4d), accompanied by a much larger shift in the vinyl sulfoxide protons (Δδ 0.7 ppm) indicating that the macrocycle is preferentially located around the vinyl sulfoxide–amide station. Furthermore, the xylylene aromatic protons of the macrocycle (H_F) appear as a diastereotopic set in **16** (Figure 4d) indicating that the macrocycle is held in a well-expressed chiral environment, i.e. in the vicinity of the asymmetric sulfoxide group.

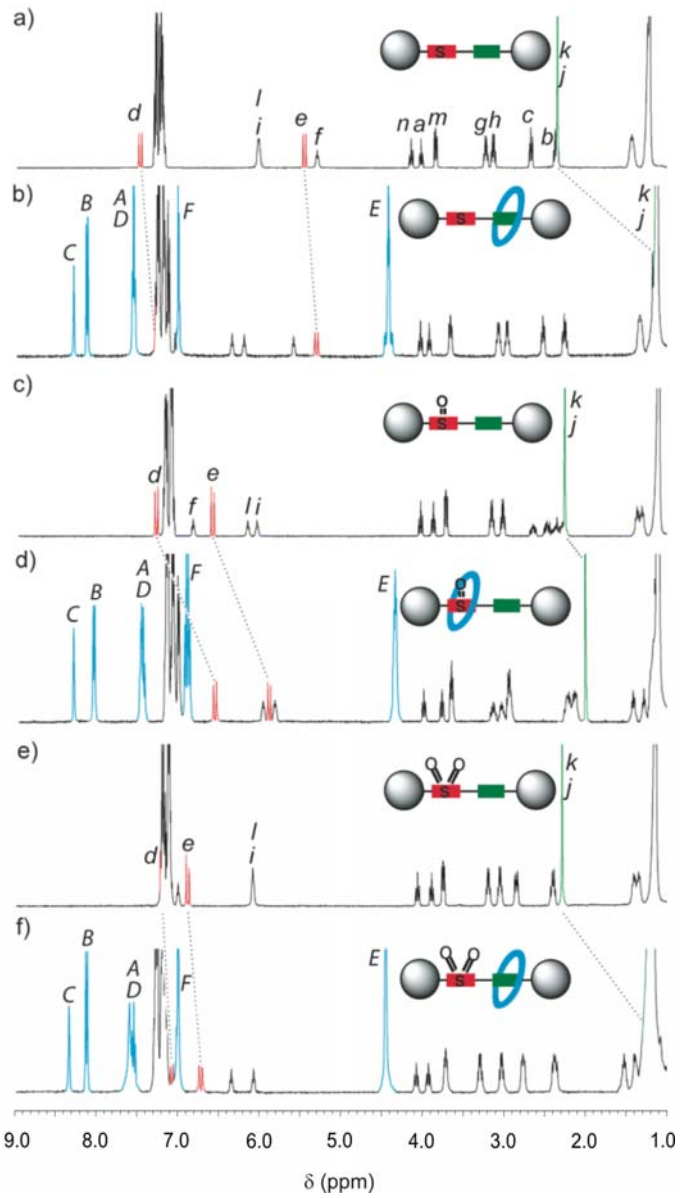


Figure 4. ^{1}H NMR spectra (400 MHz, $CDCl_3$, 25 ˚C unless otherwise indicated) of (a) sulfide thread **13**, (b) sulfide [2]rotaxane **14**, (c) sulfoxide thread **18** (55 ˚C), (d) sulfoxide [2]rotaxane **16** (55 ˚C), (e) sulfone thread **19**, (f) sulfone [2]rotaxane **17**. The assignments correspond to the lettering shown in Scheme 4.

The sulfide-, sulfoxide- and sulfone-containing rotaxanes **14**, **16** and **17** could be interconverted by oxidation and Michael-retro-Michael reactions in excellent yields (Scheme 4). Accordingly, the vinyl sulfur–amide system is a chemically-switchable molecular shuttle that could prove useful as a component of more complex molecular machines.

Conclusions

The diverse hydrogen bond accepting properties of sulfide-, sulfoxide- and sulfone-based amide threads can be effectively introduced into hydrogen bonded amide-based [2]rotaxanes through five component 'clipping' reactions. The weaker nature of amide-sulfide and amide-sulfone hydrogen bond interactions means the corresponding [2]rotaxanes are formed in lower yields than the amide-sulfoxide template and maximize amide-amide macrocycle-thread hydrogen bonding motifs in the solid state at the expense of lower energy macrocycle conformations. The sufide, sulfoxide and sulfone rotaxanes can be interconverted through oxidation, reduction and Michael-retro-Michael addition/elimination processes. As well as adding to the chemical diversity of templates available for assembling amide-macrocycle rotaxanes, these motifs can be used in the synthesis and operation of chemically-responsive bistable molecular shuttles in which the oxidation state of the vinyl sulfur group determines the position of the macrocycle in the rotaxane. The manipulation of hydrogen bonding strengths of functional groups in this way may prove useful for the construction of more complex synthetic molecular machine systems.[18d]

Experimental Section

General Method for the Preparation of Sulfur-Based Amide [2]Rotaxanes: The sulfur-containing thread (**3**, **4** or **5**, 1.0 equiv.) and Et_3N (ten-fold excess) was dissolved in anhydrous $CHCl_3$ and stirred vigorously while solutions of the amine (five-fold excess) and the acid chloride (five-fold excess) in anhydrous $CHCl_3$ were added over 3 hours using motor-driven syringe pumps. The reaction was filtered and the solvent removed under reduced pressure. The crude material was then subjected to column chromatography (silica gel, $CHCl_3$/MeOH as eluent) to give the [2]rotaxane **6**, **7** or **8** in 12, 43 or 10% yield, respectively. Further details are given in the Supporting Information.

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Supporting Information Available:

Experimental procedures and spectroscopic data for all compounds synthesized, and full crystallographic data for rotaxanes **6**-**8**. This material is available free of charge.

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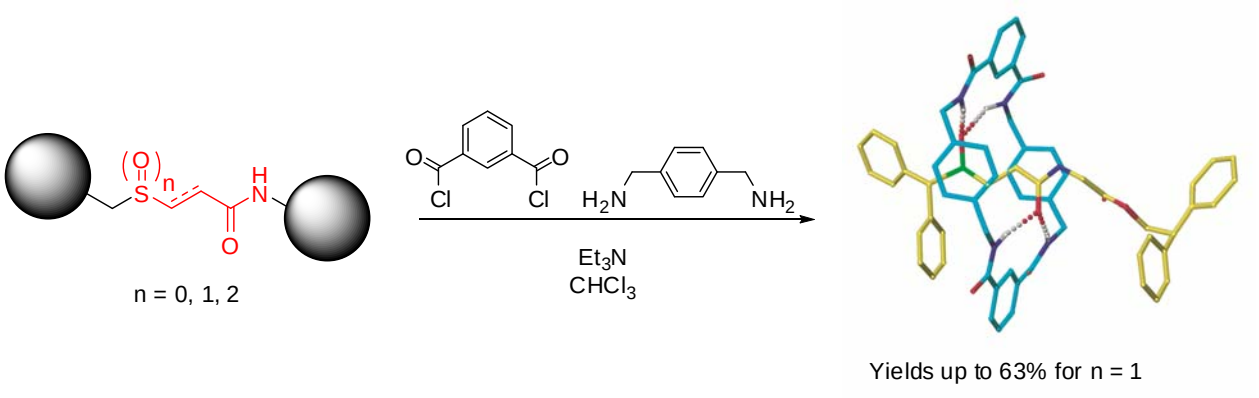
ToC graphic


n = 0, 1, 2
Et3N
CHCl3
Yields up to 63% for n = 1